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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,617	03/22/1999	JACQUES MALLET	ST96025-US	7283

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/254,617	Applicant(s) MALLET ET AL.
	Examiner Anne Baker	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[x] Responsive to communication(s) filed on *31 May 2002* .

2a)[ ] This action is **FINAL**. 2b)[x] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[x] Claim(s) *52-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[x] Claim(s) *64,66 and 70-74* is/are allowed.

6)[x] Claim(s) *52-63,65,67-69 and 75* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [x] Other: *detailed action* .

DETAILED ACTION

The response filed May 31, 2002 (Paper No. 16) has been entered. Claims 26-51 have been cancelled. Claims 52-75 have been newly added.

Accordingly, Claims 52-76 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous Office Action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating amyotrophic lateral sclerosis comprising administering to a subject by systemic administration a pharmaceutical composition comprising an adenovirus vector comprising a nucleic acid encoding a neurotrophic factor, wherein said treating results in an increased lifespan for said subject, does not reasonably provide enablement for a method of treating amyotrophic lateral sclerosis using the claimed method, wherein any treatment effect is achieved or no treatment effect is achieved. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of treating amyotrophic lateral sclerosis by systemic administration of a pharmaceutical composition comprising an adenovirus vector comprising a nucleic acid encoding a neurotrophic factor.

Given its broadest reasonable interpretation, the term "treating" encompasses prevention, cure, and amelioration of symptoms of a disease. However, the instant specification fails to provide an enabling disclosure for preventing and curing amyotrophic lateral sclerosis (ALS) because the gene therapy art is highly unpredictable, for the reasons set forth at pages 3-4 of the Office Action of Paper No. 10 (mailed 5/23/01) and reiterated herein below. Claim language adding an appropriate conclusory statement specifying the specific treatment effect that is achieved would be remedial. The specification discloses that animals receiving the claimed treatment had an increased lifespan (pages 35-42). Thus, limitation to a method that effects a treatment that results in an increased lifespan would be considered appropriate.

The specification fails to provide an enabling disclosure for the claimed method over the full scope because the specification does not provide specific guidance for producing a therapeutic effect other than an increase in lifespan, particularly prevention and cure of ALS. Gene therapy is not routinely successful and therefore the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification does not provide any guidance as to the level of gene expression required, the number of transfected cells needed, when the neurotrophic factor gene should be expressed, or the frequency of administration of the neurotrophic factor-encoding gene required to treat ALS, to produce a treatment effect other than that disclosed in the specification (*i.e.*, increased lifespan). In particular, the specification fails to provide an enabling disclosure for gene therapy of ALS wherein prevention or cure of the disease is effected. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH *ad hoc* committee to assess the

current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). Thus, absent any showing that a treatment effect other than an increased lifespan could be achieved using the claimed method, the full scope of the claims are not enabled by the disclosure.

In view of the quantity of experimentation necessary to determine appropriate parameters for the claimed method of treatment to produce treatment effects other than that disclosed in the specification, and further given the limited guidance in the specification, the limited working examples directed to producing a specific treatment effect, limited to achieving an increased lifespan in mouse models of ALS using a specific gene therapy protocol, the broad scope of the claims with regard to the treatment effect achieved, and the unpredictable and undeveloped state of the art with respect to gene therapy at the time of the invention, undue experimentation would have been required for one skilled in the art to practice the claimed method over the full scope and to use the full scope of the claimed compositions.

Applicants' arguments at pages 5-9 of the response, directed to the use of plasmids and naked nucleic acids in the method of treating, are moot in view of the amendments to the claims. The claims have been amended so that they are now limited to compositions comprising adenovirus vectors and methods of using adenovirus vectors for treating ALS.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53-60, 62, 65, 67-69, and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53-60 and 62 are indefinite in their recitation of "the adenovirus" because the term lacks antecedent basis. Claim 52 recites "an adenovirus vector," not an "adenovirus."

Claim 55 is indefinite in its recitation of "an expression cassette comprising two nucleic acids" because it is unclear how a single expression cassette can comprise "two nucleic acids". A single expression cannot comprise **two** nucleic acids. The term "expression cassette" denotes a single molecule. A single molecule cannot comprise two molecules. The genome of an adenovirus is a **single**, linear, double-stranded DNA molecule.

Claim 62 is indefinite in its recitation of "wherein the expression cassettes enable simultaneous expression of the neurotrophic factors" because the term "enable" denotes a potential property, not an actual property of the expression cassette. The term "enable" implies a conditional property, but the claims do not recite the conditions under which simultaneous expression **actually** occurs. Thus, the metes and bounds of the claim are not clearly set forth.

Claim 65 is indefinite in its recitation of "a cassette enabling simultaneous expression of two different neurotrophic factors" because the term "enabling" implies a conditional property, but the claims do not recite the conditions under which simultaneous expression actually occurs. Thus, the metes and bounds of the claim are not clearly set forth.

Claims 67-69 and 75 are indefinite in their recitation of "the adenovirus vectors comprise two replication defective recombinant adenoviruses" and "wherein at least one adenovirus vector is a replication defective recombinant adenovirus" because an adenovirus vector is different from an

adenovirus. Furthermore, it is unclear how adenovirus vectors can **comprise** two adenoviruses.

Amendment to the claim substituting "are" for "comprise" is suggested.

Conclusion

Claims 64, 66, and 70-74 are allowable. The prior art does not disclose or fairly suggest a pharmaceutical composition comprising two adenovirus vectors, wherein each vector comprises a nucleic acid encoding a different neurotrophic factor.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER